REMARKS

Claims 1 and 2 are pending in this application. Claims 3 and 4 were previously cancelled without prejudice or disclaimer. Claims 5-10 have been withdrawn from consideration as being drawn to a non-elected species.

1. Claim Rejections Under 35 U.S.C. § 103

The Examiner rejects claims 1 and 2 over Randall et al., Vaccine. 1993 Sep;11(12):1247-52 (hereinafter 'Randall') in view of Harlow et al., Antibodies. A Laboratory Manual. 1988. pages 139-147, as unpatentably obvious. Applicants respectfully disagree and traverse as follows.

The Examiner concludes that, "Randell [sic] et al. clearly teach anti-sera made by immunizing mice using histidine tagged antigen, contains antibody against N-terminal histidine tag..." Final Office Action of January 23, 2007, p. 3, lines 23-24. Moreover, the Examiner argues that Randall teaches, "anti-sera contains [sic] antibody against N-terminal histidine tag for purification of protein comprising histidine tag...". Final Office Action of January 23, 2007, p. 4, lines 9-10.

However, Randall does not teach or suggest any monoclonal antibodies let alone those against fusion proteins comprising a histidine portion wherein the monoclonal antibody binds specifically to the histidine portion but not to the non-histidine portion of the fusion polypeptide, and wherein the histidine portion comprises 6-18 histidine residues.

In order to bridge the shortcomings of Randall, the Examiner cites Harlow's generalized methods of monoclonal antibody production as rendering the claimed invention unpatentably obvious.

Applicants respectfully yet strenuously disagree with the Examiner's conclusions.

1.1. Randall Generally

Randall is concerned with the production and isolation of recombinant full length simian immunodeficiency virus ('SIV') enzymes p17 and reverse transcriptase ('rt') to study their suitability as potential vaccine components. In order to ensure that only full length proteins are isolated, the authors generated recombinant proteins that could be isolated in a two-step process that exploited specific exogenous amino acid sequences at their N- and C-termini.

Specifically, the authors generated recombinant proteins in which the two proteins each have an N-terminal oligohistidine tag and a C-terminal Pk tag ('His-p17-Pk' and 'His-rt-Pk'). The N-terminal tag consisted of twelve amino acids including an array of six histidines which facilitated the binding of the recombinant proteins to nickel.

The recombinant proteins were isolated in a two-step process, *i.e.*, the "dual tag' affinity approach. First cell lysates were run through a nickel affinity column in which the N-terminal oligohistidine tagged recombinant proteins were immobilized. The bound oligohistidine tagged recombinant proteins were then eluted. In the second purification step, the eluate was run through an affinity column coated with anti-Pk antibody, *i.e.*, mAb SV5-P-k, which bound the C-terminal Pk tag. The bound recombinant protein was then again eluted. This ensured that that only recombinant proteins having both the N- and C-terminal tags were recovered.

Recombinant rt or p17 protein isolated in this way was then used an immunogen to generate an antibody response in a mouse. Polyclonal anti-His-p17-Pk and anti-His-rt-Pk sera were then isolated and tested for specificity and potential cross reactivity with one another's antigens.

1.2. Randall's Alleged Disclosure of Anti-His Tag Antibodies is Speculative and Vague

The Examiner concludes that, "Randell [sic] et al. clearly teach anti-sera made by immunizing mice using histidine tagged antigen, contains antibody against N-terminal histidine tag..." Final Office Action of January 23, 2007, p. 3, lines 23-24. A careful reading of Randall, however, reveals that the authors' statement about the alleged presence of anti-His antibodies in the anti-sera made by immunizing mice with histidine tagged antigen is pure speculation.

Specifically, the Western blot in Figure 5d does not appear to show **any** discernable label present in either of its columns #1 (His-p17-Pk probed with anti-His-Rt-Pk serum) or #2 (His-P17 probed with anti-His-Rt-Pk serum). As such, it in effect appears to show the opposite of what the Examiner asserts: that sera raised against His-rt-Pk does not react with His-p17-Pk or His-p17. In other words, Figure 5d of Randall actually appears to show that there exist no anti-His antibodies in the sera raised against His-rt-Pk.

Notwithstanding the lack of signal in Figure 5d or any other published physical evidence, Randall nevertheless reports observing some presumably label in Figure 5d. Randall states that sera raised against His-rt-Pk reacted with the, "large N-terminal fragment of His-p17-Pk from which the C-terminal [Pk] tag had been removed *(Figure 5d)*." (hereinafter '**sentence B**'), p. 1251, right column, lines 2-4. In order to dismiss and explain away the artifact the authors allegedly observed (but do not show) in Figure 5d, Randall speculates that, "[a]ntibody against the N-terminal His tag could also be detected in the anti-His-rt-Pk sera." (hereinafter '**sentence A**'), p. 1251, right column, line 12 to left column line 2.

However, Randall provides absolutely no proof that anti-His antibodies are the source of the artifact the authors allegedly observe in Figure 5d. In fact, **authors do not show and provide no way of determining** whether the anti-His-rt-Pk serum supposedly binds the His-

p17's fragment's p17 portion, the six His residues or the six non-his residues at the N-terminus, epitopes that may have been generated on His-p17 by the digestion of His-p17-Pk with thrombin, or any combination of these classes of epitopes.

Reflective of the authors' speculation, Randall states in a subsequent sentence that, "**[n]evertheless, it is clear** from these results that the predominant antibody response in the immune sera was against the SIV portion of the fusion proteins..." (hereinafter '**sentence C**'), p. 1251, right column, lines 5-9.

Sentences A, B and C come directly after one another. Therefore, sentence C's use of the clause, "**[n]evertheless, it is clear**" negatively modifies immediately preceding sentences A and B. In other words, whereas it is "clear" that results showed that anti-Rt and anti-p17 antibodies were generated, **it is not at all clear** that the alleged artifact (mentioned in sentence B) is actually reflective of bona fide binding, or whether the speculative conclusion that anti-His antibodies are present (sentence A) is correct. Therefore, Randall's speculative conclusions about anti-His-Rt-Pk serum's alleged cross reactivity with His-p17 are vague and ambiguous at best.

Applicants respectfully submit that the skilled artisan would not have concluded that Randall clearly disclosed anti-His antibodies at the time of filing of the subject application. At the time of filing, the scientific literature there were examples of the enigmatic immunogenicity of HIV proteins. For example, Liang et al., J Immunol Methods. 1990 Aug 28;132(1):57-62, (Tab A) showed how antibodies raised to one HIV protein also cross-reacted with other HIV proteins.

The information one of skill in the art would have gleaned from the literature and Randall et al., at the time of filing of the subject application cannot now be retroactively altered by a

statement made by Dr. Richard Randall in 2004 at the behest of the Applicants' legal opponents in the context of a European Opposition proceeding in a related European Patent Application No. 0815141.

During those proceedings, Dr. Randal provided a blown up version of the Randall et al. paper's Figure 5 (Tab B) as well as a second autoradiograph that was generated by a longer exposure (Tab C). Dr. Randall stated that:

> Figure 5d of the paper shows that the anti-His-rt-Pk antiserum crossreacts with a SIV p17 polypeptide which has a N-terminal His tag (His-p17). A weak signal is present on a Western blot when the anti when the anti-His-rt-Pk antibody reacts with His-p17. The most likely explanation for this **is** that mice immunized with His-rt-Pk produce small amounts of antibodies to His tag. Randal Declaration; Tab C at para. 4. [emphasis added]

It must be kept in mind that obviousness under 35 U.S.C. §103, is measured at the time of filing, in this case March 1995. Dr. Randall's declaration says nothing about what one of skill in the art would have thought about the results in Randall et al., in March 1995. The declaration of Dr. Randall was executed in 2004 and only provides evidence as to what one of skill in the art might have thought as of that date, i.e., it is written in the **present tense.**

Again, Dr. Randall's conclusion that the "most likely explanation" for the signal he supposedly perceived in Figure 5d, "is that mice immunized with His-rt-Pk produce small amounts of antibodies to His tag" is only effective as of March 2004. In effect it appears that Dr. Randall altered this characterization of the potential presence of anti-His antibodies from vague speculation in 1993 to being, "[t]he most likely explanation" in 2004.

It should come as no surprise, if the scientific movement from speculation in 1993 to "[t]he most likely explanation" in 2004 was facilitated by Dr. Randall's knowledge of the existence and the commercial success of the inventors' anti-His antibody in 2004.

Taken together, Applicants respectfully assert that any alleged disclosure of anti-His antibodies in Randall et al., prior to the filing date of the subject application, can only be characterized as vague, speculative and ambiguous and certainly not "clear" as argued by the Examiner.

1.3. Randall Teaches Away From the Claimed Antibodies

Assuming *arguendo* that the vague, speculative and ambiguous disclosure of polyclonal anti-His antibodies in Randall et al., were "clear" as alleged by the Examiner, Randall teaches away from the idea of pursuing the claimed monoclonal anti-His antibodies.

The Examiner argues that Randall teaches, "anti-sera contains [sic] antibody against N-terminal histidine tag for purification of protein comprising histidine tag...". Final Office Action of January 23, 2007, p. 4, lines 9-10. This is clearly incorrect as Randall does not teach or suggest purifying recombinant proteins using the anti-sera generated in the experiments. Moreover, no where does Randall disclose purifying his-tagged proteins with an antibody to a His-tag.

Randall states that, "a short oligohistidine tag can be purified by nickel-affinity column chromatography under both native (non-denaturing) conditions and in 6M guanidium – HCL or 8M urea" p. 1248, left column, lines 47-50. As such, Randall states that a His-tagged protein can be readily purified without having to first source an expensive and potentially cross reactive and contaminating antibody.

In fact, the whole reason why Randall used a His-tag rather than any other epitope, e.g., myc-epitope, Flag-epitope or any other epitope, for which specific antibodies were readily available, was that His-tags are not likely to be immunogenic. This was of great benefit because previous moeties, i.e., glutathione-S-transferase, were too immunogenic and interfered with the

immune response to the tagged protein. Moreover, His tags are small and "[o]bviously, the shorter the tags the less likely are the chances that they would interfere with the immunogenicity of the recombinant antigen." p. 1248, left column, lines 41-44.

Therefore, given the disclosure of Randall, one of skill in the art would have been dissuaded from taking on the arduous task of attempting to make the claimed monoclonal antibodies against a target that is not likely to be immunogenic particularly where His-tagged proteins would already be easily purifyable using a nickel column – without the need for an antibody in the first place.

Moreover, even if polyclonal His-tag antibodies existed in the His-Rt-Pk antiserum tested in Figure 5d, Randall's discussion of His-tags would teach the skilled artisan that His-tags would be insufficiently immunogenic to generate sufficient antibodies to be of use in purifying His-tagged proteins as a substitute for a highly efficient nickel column. Therefore, reading Randall, the skilled artisan would have considered the idea of purifying His-tagged proteins using an affinity column coated with anti-His antibodies – given the low immunogenicity of the His-tag – to be scientifically inefficient and economically wasteful.

It should, therefore, be of no surprise that Randall et al., not only speculated about the existence of anti-His antibodies (as an experimental artifact) but ignored their potential significance. The Inventors, however, recognized the potential applications for the claimed anti-His antibodies. They also developed a method for generating high affinity anti-His monoclonal antibodies that specifically detect His-tags despite their low immunogenicty.

1.4. Products Convered by the Claims Have been Commercially Very Successful

Assuming *arguendo* that the Examiner has proffered a legitimate *prima facia* case of obviousness for rejecting the claims at issue under 35 U.S.C. §103, Applicants respectfully

submit any such case is rebutted by the commercial success of products failing under the claims at issue.

The present patent application is exclusively licensed to Qiagen GmbH. Qiagen is one of the World's largest providers technologies and products for preanalytical sample preparation and molecular diagnostics.

Since licensing of the subject application, Qiagen has sold several million dollars worth of products that fall within the scope of the present claims. These products include Qiagen's Penta.His HRP Conjugate Kit, RGS.His HRP Conjugate Kit, Tetra.His HRP Conjugate Kit, Penta-His Biotin Conjugate, Penta-His Alexa Fluor 532 Conjugate, Penta-His Alexa Fluor 555 Conjugate, Penta-His Alexa Fluor 647 Conjugate, Penta·His Antibody, BSA-free, Tetra·His Antibody, BSA-free, Anti·His Antibody Selector Kit, RGS·His Antibody, RGS·His Antibody, BSA-free, Ni-NTA Fast Start Kit.

Moreover, Qiagen has successfully sublicensed this patent application to number of distributors around the world.

Accordingly, Applicants respectfully submit any *prima facie* case under §103 proffered by the Examiner is rebutted by the commercial success of products failing under the claims at issue.

CONCLUSION

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDermott Will & Emery LLP

Thomas A. Haag, Ph.D., Esq.
Registration No. 47,621

600 13th Street, N.W.
Washington, DC 20005-3096
Phone: 202.756.8000
Facsimile: 202.756.8087
Date: September 19, 2007

Please recognize our Customer No. 20277 as our correspondence address.